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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/812,991	Applicant(s) Nestor
	Examiner Mark L. Berch	Group Art Unit 1611

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *23-28* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *23-28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-28 are rejected, 35 U.S.C. 102(b) as anticipated by Beauchamp.

Note Formula I in U.S.P. 5,043,339, since one of R and R^1 must be an amino acid, the genus describes basically mono- and diesters (depending on whether 1 or both of R, R^1 are amino acids). The preferred amino acids are listed at col. 2, lines 23 as glycine, alanine, valine, and isoleucine. This also happens to be the only amino acids used in the examples. Both mono and diesters are prepared; See Ex. 6. This than gives 8 choices; four monoesters and 4 diesters. There are 2 preferred choices for B, cytosine, and ganciclovir (col. 2, line 14). Again, these are the two bases of the examples. This then produces 8 X 2=genus of 16. Such a small genus legally constitutes anticipation of all its members, thus anticipating the ganciclovir mono ester with valine (In re Sivaramakrishnan, 213 U.S.P.Q. 441 [genus of 70]; In re Petering, 133 U.S.P.Q. 275 [genus of 20]; In re Schaumann, 197 U.S.P.Q. 5 [genus of 14]. The utility is the same.

Applicants' traverse in the parent focused on the term "crystalline". The reference is silent as to whether such compounds are or are not crystalline.

Not here - no crystalline!!

Basically, art rejections cannot be avoided simply by describing their compound in greater detail than the prior art, and that is exactly what "crystalline form" argument does. Suppose, for example, that the examiner had a reference which had a claimed species in crystalline form, just as the claim required. Then suppose the claim were amended to say that the compound "melts at 200-202°C" or "has a refractive index of about 1.4" or "has a specific gravity about 1.3", etc. This language of course merely describes the same compound more fully. According to applicants' reasoning presented in the parent, since there is no teaching in the reference of any compound having e.g. a specific gravity of around 1.3, this amended claim should be free of any art rejection, even though the amended claim is still describing the same thing. Thus, this reasoning would allow virtually any anticipation to be overcome. Indeed, one could patent the same compound again and again, each time describing it in greater detail. That is, no matter how fully a compound is described in the prior art, the rejection could always be overcome by finding some physical (or biological, etc.) property that wasn't mentioned at all. Similarly, the compound could be claimed repeatedly by adding fresh characteristics.

Similarly, if Appellants' reasoning were accepted, the "Petering type" anticipation would become essentially meaningless. Any applicant could overcome this type of rejection by attaching to the claim an essentially trivial limitation. Applicant could add the limitation of "solid" or "which does not decompose in air" or "which does not have a melting point of 97 °C". Such limitations would, as a practical matter, not meaningfully limit the scope of claim protection. But, by this reasoning, it would overcome a "Petering

type" anticipation, since in such circumstances, there never is any physical data. The PTO would then have the impossible burden of then having to show that the prior art species would not inherently have the property of a melting point other than 97 °C. This burden is impossible because the PTO has no testing facilities, and one cannot reason a melting point.

Furthermore, Appellants' reasoning of placing the burden on the PTO would operate in ordinary anticipations where the reference actually named the compound, but gave no data. According to this reasoning, any of the above limitations would still overcome the rejection. Applicant could still add the limitation "which does not have a melting point of 97 °C" and argue that, as did applicants in the Reply Brief in the parent: "it is incumbent on the PTO to establish inherency" of this "which does not have a melting point of 97 °C" limitation. Furthermore, even if the reference prepared the compound and reported the melting point, reported that the compound did not decompose in the air, and was a solid, applicant could add further limitations, such as that it is crystalline. Applicant could then argue, as the Reply Brief in the parent did, that the reference "does not disclose crystalline" material. If the reference actually did disclose that the compound was crystalline, applicant could add limitations that the compound "does not form hexagonal plates" (or does not have some very rare form), has or does not have a given specific gravity, refractive index, solubility in water etc. No matter how well described the compound was in the prior art, applicant could find some aspect of the material that wasn't described, and then argue that the reference does not disclose (i.e. was silent about) that characteristic.

That is why the burden is on applicant to show that the prior art material lacks that property.

Similarly, if a reference simply named a compound i.e. gave no physical properties at all, the anticipation could then the overcome with any physical language e.g. "solid" or "does not decompose at room temperature."

Appellants in the parent correctly pointed out that the Examiner's argument assumes that this is just a matter of describing an old compound more fully, i.e. "that crystallinity is an inherent property of GMHV." All inherency-type rejections made by the PTO are based on an assumption, because the PTO has no testing facilities. And this testing burden cannot be placed on the PTO (Cf. *In re Brown*, 173 U.S.P.Q. 685, 688). The examiner is mindful of the fact that there have been occasions when a compound thought to the inherently non-crystalline was crystalizable by a method that applicant devised, and hence such a limitation did indeed distinguish over the prior art. But applicants do not assert this, nor do they assert that their crystallization technique is out of the ordinary. Instead, they simply rely on a lack of disclosure of property. But lack of knowledge of a property does not alone defeat inherency (Cf. In re Wilder, 166 U.S.P.Q. 545, 549).

In the parent, applicants also cited *Ex Parte Levy,* 17 USPQ2d 1641, 1463-4. However, the anticipation in that case was based on a very different factual situation. The claim required a "biaxially oriented catheter balloon". However, the decision states, " Moreover, it would appear to be undisputed that the only method disclosed by Schjeldahl for transforming the biaxially oriented starting plastic into the final catheter balloon, i.e.,

injection blow molding, is not capable of producing a biaxially oriented catheter balloon. In fact, it is undisputed that injection blow molding would destroy the biaxial orientation of the plastic starting material." In order to get around this problem the Examiner conjured up a stretching step. But there was no direction in this reference for a stretching step. Instead, the decision note, " We have only a general invitation to employ "injection blow molding." As previously discussed, it is undisputed that injection blow molding would not have produced a biaxially oriented balloon and would have destroyed the biaxially orientation of a polymeric starting material." Here, by contrast, it is not the case that the methods of the reference are incapable of producing a crystalline form.

Applicants also cited *Hansgirg v. Klemmer,* 40 USPQ 665, 667, for the notion that inherency cannot be established by "probabilities or possibilities". But that isn't really relevant. The prior art species either is or is not capable of being crystallized. This isn't a circumstance where one can say that a given reaction has, say a 50% chance of being capable of producing a given product and a 50% chance of not being capable.

Applicants also raised the issue of physical form. The examiner has never taken the position that physical form is irrelevant to patentability, and it is of course true that, under some circumstances, that a different form can make an old material patentable. But Applicants have not shown that the form is different. Thus, Applicants cited *In re Cofer,* 148 USPQ 268, where claims to "free-flowing crystals" were permitted. The prior art had been disclosed as a glassy solid. Here, the prior art was definitely different (hence the 35 USC 103 rejection). Exactly the opposite is true here --- there has not been established that this

is in any way different than what the prior art would obtain. Indeed, given the prior art compound as prepared previously was not crystalline, and that none of the related compounds cited were anhydrous, and the presence of two references showing that "anhydrous ATMP could not have been predicted from what was known in the art"(the prior art in fact taught that what is crystallized with this category of salts is the mono- or di-hydrate) the Court held that "such a disclosure would not provide a basis for predicting with reasonable certainty that ATMP could exist in crystalline anhydrous form." Such is not the case here; no such record exists here. The court concluded "we are not convinced by this record that it would have been obvious *how* this could be achieved." The reference, in effect, was held to be non-enabling, in view of the failure of others to achieve this.

Similar is *In re Irani,* 166 USPQ 24. There, the prior art was only known as a glassy solid. There, the rejection relied on *Ex Parte Hartop,* 139 USPQ 525 for a general proposition that form does not matter, which is not a position that the examiner here takes. Further, the reference taught a viscous liquid, and there was a declaration to the effect that the compound was known only as a viscous liquid. No such fact pattern exists here.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the

prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-28 are rejected, 35 U.S.C. 103 as obvious from Beauchamp. The reasoning is the same as above, except that here the examiner argues that the crystalline form is obvious.

Ex. 5 is the closest species, as this is the valinate, albeit the bis, not mono, validate Col. 10, line 44 says that the glass "turned into a solid on scrapping". The reference is silent as to whether the solid is crystalline or amorphous. However, even if this material is not crystalline, as appellant points out, crystallinity is usually a desired feature. Hence, one skilled in the art would be motivated to obtain it using conventional methods (e.g. recrystallization). However, if applicants can show that all efforts (short of undue experimentation which is not required) fail to produce a crystalline form, i.e. that the diester does not inherently crystalline under suitable conditions), then "crystalline" claims would be deemed unobvious from the reference.

Applicants' arguments in the parent again relied on the lack of "disclosed crystallinity" or that there is no language "indicating possession of any crystalline compound". It is correct that the reference is silent. The products are called solid (e.g. Ex. 5) or powder (e.g. Ex. 4a), which may or may not be crystalline. But appellants do not do deny that crystallinity is a desired property, so even if these solids are not crystalline, obtaining the material in such a form would be a routine expedient.

Applicants also argued that this is an "obvious to try" situation. It is not. *In re O'Farrell,* 7 USPQ2d 1673 discussed the two types of obvious to try situations. First, "...to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many choices is likely to be successful." Obviously, that is not the case here. Ordinarily, if a material is crystalline, it will form under standard crystallizing conditions, such as dissolving in one solvent and adding a precipitating solvent to this solution. Such procedures are normally employed to purify compounds, wherein the material is obtained in crystalline form even without any intention to actually do so. There is no reason to think that this compound requires special procedures, and indeed, judging from the specification, page 29, lines 9-18, no special procedures are needed. The second circumstance is "to explore a new technology or general approach that seems like a promising field of experimentation where the prior art gave only general guidance." This is clearly not the case either. Ordinarily, crystallizing an organic compound is hardly a matter of a "a new technology or ... promising field of experimentation".

Moreover, contrary to the argument made in the Reply Brief in the parent, the fact that "crystallinity is a desired property" is not "irrelevant"; it goes directly to the point of motivation, which is always relevant in an obviousness rejection.

Claims 23-28 are rejected as obvious, 35 U.S.C. 103 from Verheyden in view of Beauchamp (1992).

The claimed species is the valinate ester of ganciclovir.

Ganciclovir, taught in the primary reference, is extremely similar in structure to acyclovir. Their structures are indeed identical, except that acyclovir has one hydroxy methyl attached to the methoxy methyl side chain and Ganciclovir has two. Both are antivirals used to treat herpes infections. Hence, one skilled in the art would find it reasonable to infer information from one about the other. The difference is so small (one hydroxymethyl versus two) that if these are not analogous, then what is? The entire rest of the molecule, as well as the utility, is the same.

Beauchamp (1992) teaches that of all the amino acid prodrugs tested with acyclovir, the L-valyl ester "was the best prodrug". It gave 63% urine availability as opposed to 19% for the parent drug. One skilled in the art would be motivated to obtain this enormous improvement with Ganciclovir too by preparing the L-valyl ester of gangciclovir in order to obtain a comparable improvement.

With regard to hydrochloride, Method A of the secondary reference gave the salts as hydrochlorides (see page 159, col. 1, 14th from last line). Crystalline form is inferable from the use of "recrystallize" in the Method A synthesis, and would at any rate be obvious for reasons set forth in the above discussion.

Applicants in the parent first argued "There is neither disclosure nor suggestion in Verheyden et al. of any esters of ganciclovir."

This is true, but the rejection is not over Verheyden alone.

Next, applicants attacked the reasoning:

"While acyclovir valinate is a suitable prodrug of acyclovir, this does not lead to the conclusion that GMV is a suitable prodrug of ganciclovir."

First, the word "suitable" understates the teaching of the reference. The reference teaches that the valinate was the best prodrug form, giving results much better than the parent drug. Second, the Examiner does not have to come to a "conclusion". The rejection only requires that one be motivated to do the combination. A rejection under 35 U.S.C. 103 does not require a conclusion that it will surely work (In re Lambert, 192 U.S.P.Q. 278; In re Kronig, 190 U.S.P.Q. 428; In re Rinehardt, 189 U.S.P.Q. 143; In re Longi, 225 U.S.P.Q. 645, 651), but only a reasonable expectation of success. The motivation is clear. The use of valinate prodrug gave a huge improvement with acyclovir, so one would be motivated to obtain a comparable improvement an antiviral of almost identical structure.

Next, applicants addressed the question of mono and bis esters:

"Esterification of ganciclovir, without some specific procedure involving blocking of one of the two hydroxy groups or a method of selective de-esterification, will tend to produce the bis-ester or at best mixture of the mono- and bis-esters, which is not the crystalline GMVH of the claims."

This is all true, but how does this defeat obviousness? The two procedures (Blocking or selective deesterification (more precisely, mono-deesterification, since the two positions are equivalent) are known in the art. But even if not, esterification will produce a mixture of mono and bis esters. The ratio will of course depend on the relative amounts of reagent. The fact that the diester is also obvious does not mean that the monoester isn't obvious. Indeed, Beauchamp (1992)'s esters are (necessarily) monoester, which would certainly put in mind to monoester.

The analogy to a bicycle is not a good one. Bicycles are well known to require both tires be inflated. No such knowledge exists here. The secondary reference establishes the desirability of the valinate prodrug. Either mono- or di-would be obvious.

Finally, applicants argued that does not suggest the "finding of crystallinity". But the general desirability of crystalline materials and the material being "recrystallized" is sufficient to make this obvious.

Along with the Reply Brief in the parent, applicants attached a "Memorandum of Record". Appellants have done a "further side-by-side comparison." In the event that applicants opt to submit such a document in this case, it must be pointed out that data not in proper affidavit form cannot overcome an obviousness rejection. Moreover, the discussion leaves a lot to be desired. The explanation as to why these numbers are different from those presented early is simply too vague. Note that 54.9% bioavailable is radically different from the early description of "practically completely bioavailable". The focus on

the bisvalinate is misplaced; as has been stated previously, there is no rejection over the bisvalinate.

Claims 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for CMV, does not reasonably provide enablement for treating herpesviruses generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The rejected claims call for the treatment of herpesviruses generally. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the treatment of herpesviruses generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case.

By way of background, it should be noted that new herpesviruses are being discovered all the time. Approximately 100 have been isolated so far, which include 8 human ones. The family is divided into 3 subfamilies. There are the alphaherpesvirinae, which include the simplexviruses HSV-1 and HSV-2 (i.e. HHV-1 and HHV-2), and the genus varicellovirus, Varicella Zoster Virus, i.e. HHV-3. There are the betaherpesvirinae, which include the genus cytomegalovirus, CMV, i.e. HHV-5 and the roseolovirus genus, with HHV-6 and HHV-7. There are the gammaherpesvirinae, which include the genus Lymphocryptovirus, EBV, i.e. HHV-4 and the Rhadinovirus, HHV-8. The non-human

herpesviruses generally fall into these subfamilies as well, e.g. mouse cytomegalovirus, which is a muromegalovirus in the betaherpesvirinae subfamily, or SVV, one of the alphaherpesvirinae . It should also be noted that Simian B virus, while considered a non-human virus, is capable of infecting simian handlers, causing among other things meningoencephalitis. Herpesviruses are similar is terms of virion structure but are widely separated in terms of genomic sequence and proteins. They have no common antigens. Their shape is unusually complex. A proteinaceous core has a large DNA genome wrapped around it, all in a toroid shape. This is inside an icosahedral capsid with 162 hexagonal capsomers. Outside this is an amorphous, proteinaceous region called the tegument. Surrounding this is the envelope with at least 9 associated glycoproteins. These proteins appear to be individually dispensable for infectivity, and herpesviruses appear to have available more than one route for penetration.

Although several drugs have been developed which are effective against one or a few herpesviruses, no one has been able to get any of these drugs to work generally. The same is true for animal herpesviruses, except that these are a lot more numerous. In the herpes family, in vitro suppression often does not translate into actual usefulness.

Consider for example EBV. This is the virus linked to infectious mononucleosis (IM); nasopharygeal carcinoma; Burkitts lymphoma; Post-transplantation lymphoproliferative disease (PTLD), which exists in 4 B-cell forms and in some T-cell variants as well; and other T-cell lymphomas including Benign Lymphocytosis and Purtillo syndrome; some thymomas; and hairy leukoplakia. There are a few antiviral which will

rather weakly suppress EBV replication. However, the skill level in this art is so low, and the difficulty of the task so high, those skilled in the art are unable to get such drugs, e.g. Acyclovir to provide therapeutic benefit. The most important disease linked to EBV is of course IM, a disorder which is invariably listed as untreatable.

Moreover, there is much more covered here than EBV. HHV-8 is now recognized as the causative agent for Kaposi's Sarcoma, the most important AIDS-related neoplasm. There is no treatment for this.

The claimed compound is a prodrug of Ganciclovir. Thus, it is presumed to be effective against what Ganciclovir is effective against, viz, CMV. Thus, a claim which covered e.g. EBV, HSV, HHV-8, etc, would not be enabled.

Finally, it should be noted that:

A. Even if in 1997 or 1998, one of ordinary skill in the art was finally able to figure out how to get Ganciclovir to work generally against herpesviruses, the parent date is 5/94, (or 7/94 for the original filing) so that one must show that such skill level existed then, an impossible task.

B. There is no evidence for such an effect for this prodrug either.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter.

See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 23-28 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 51-56 of copending Application No. 08/453,223. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The claims are identical to those of the parent.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718.

Mark L. Berch

Primary Examiner

Group 1610 - Art Unit 1611

April 30, 1998